PRELIMINARY REPORT OF THE COMBINED TREATMENT OF PULMONARY TUBERCULOSIS WITH OLD TUBERCULIN AND INH

AUTHOR(S):

TOKIWA, Tasuke; TERAMATSU, Takashi

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Tasuke TOKIWA* and Takashi TERAMATSU**
常盤太助　　寺松孝

* *From National Kyoto Sanatorium*
** *From the Surgical Division of Tuberculosis Research Institute, Kyoto University*

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It is well known that tuberculous caseous lesions have a tendency not to be easily absorbed or cicatrized in spite of the use of current effective antituberculous agents.

Also this tendency seems to be more conspicuous in sclerotic caseous lesions than in nonsclerotic lesions.

As is well known, the tuberculous lesion is characterized by caseation and capsulation.

According to our experimental studies, the caseous matter in the sclerotic lesion is so hard that it is not easily absorbed[1,3,7] and also the capsule of the lesion is refractory to being easily digested or destroyed[3,8]. These characteristics of caseous matter and capsules may be the reason for their stability and at the same time they inhibit the absorption or cicatrization of the caseous lesions[5].

Furthermore, we have experienced that when the pre-caseous tuberculous lesions are irritated in the early stages, acute exudative inflammation in the lesions is increased or appears again and caseation doesn't occur. When moderate irritation is given repeatedly to such lesions combinied with chemotherapy, the lesions often attain cicatricial healing without any caseation.

Also when some old stage lesions are repeatedly irritated, in which caseation already occurred acute inflammation again takes place in the lesion, causing the capsule of the lesion to be digested or destroyed by the infiltrating cells and the softening or liquefaction of caseous matter begins. If such repeated irritations are combined with chemotherapy, the possibility of cicatricial healing of these old lesions is much improved[5].

From thes results, it may be reasonable to expect that the "irritation therapy", if adequate irritants were used, and if combined with chemotherapy, promotes

the softening and cicatrization of tuberculous caseous lesions.

Therefore, we have looked for such adequate irritants since 1957. We have examined glycyrrhizin, old tuberculin, cortisone, X-rays, ultra-short wave, etc. experimentally in order to establish their value as irritating agents and have reached the conclusion that glycyrrhizin and old tuberaulin are suitable for our purposes[2,5].

Then we have studied clinically their irritating effects. The clinical effect of glycyrrhizin has already been reported in a former article[5].

In this paper, the clinical effects of the combined therapy of old tuberculin with INH will be reported and the value of old tuberculin as an irritating agent from our clinical and pathologic-histological results will be discussed.

1. Material and method.

The combined therapy with old tuberculin and INH has been performed on 58 cases since 1960.

Old tuberculin was given in many ways. INH was given with daily dose of 0.5 g during observation periods in all cases.

In this article, the results of 18 cases among 58 will be reported, because the results of these 18 cases who could be given regularly with 0.5 c.c. of 1000× old tuberculin intramuscularly twice per week for to 3 months were more prospective than the results of other ways and the pathologic and histopathologcal investigations about 5 resected lungs of this group could be performed.

In all 18 cases no improvement had been recognized 6 or more month's chemotherapy alone, when the combined therapy with old tuberculin and INH was started.

5 cases of 18 cases were operated with pulmonary resection at 2 or 3 months after the combined therapy. The other 13 cases were observed clinically without any operation.

2. Clinical and pathologic-histological results and discussion.

5 cases who were operated with pulmonary resection, as shown in Table I, had been treated with chemotherapeutics in the past and their X-ray findings prior to the combined therapy did not change for 6 or 10 months.

X-ray findings of 2 cases (Case I and Case II) of 5 cases (operated) having sclerotic cavities in the right upper lobe at the beginning of treatment are as shown in Fig. 1 and Fig. 2.

After 2 to 3 month's coumbined treatment, their X-ray findings were improved as shown in Fig. 3 and Fig. 4.

Table I. Five Cases who were performed Pulmonary Resection after the Combined Therapy with old Tuberculin and INH.

Case	Chemotherapy in the Past				Unimproved Period in Radiographical Finding prior to Tuberculin and INH Therapy (M)	The Combined Treatment with Tuberculin and INH		
	Period (M)	SM (g)	PAS (g)	INH (g)		Type of Lesion at the Beginning	Period (M)	Radiographic Improvement
I	64	104	11700	110	6	Sclerotic Cavity	2.5	+
II	27	264	9900	96	10	Sclerotic Cavity	3	+
III	24	26	3600	144	10	Sclerotic Cavity	3	—
IV	10	78	2700	100	6	Sclerotic Cavity	2	—
V	14	60	2000	80	6	Sclerocaseous Lesion alone	2.5	—

The resected lungs of them are shown in Fig. 5 and Fig. 6. It is seen the tendency of remarkable cicatricial healing in their cavities, and the bleeding tendencies in the cavity wall, particullary in the necrotic layer.

We know that in the cases of sclerotic cavity who were treated with antituberculous agents alone for long time, the cell infiltration is decreased in their cavity wall, or necrotic tissues and capillary formation and cell infiltration in the caseous lesions are generally very poor. (Fig. 7).

On the contrally, in these 2 cases remarkable multiplication of new capillaries and cell infiltration in the cavity wall are observed. (Fig. 8, 9)

The remaining 3 cases did not show any radiographical improvement, but in their resected lungs could be seen microscopically the multiplication of new capillaries, cell infiltration and bleeding tendencies in any parts of the capsule of lesions. (Fig. 10)

These microscopic findings show that the destruction of the lesion capsules is going on, which is not so common in the cavity wall treated with antituberculous agents alone.

Moreover in these 3 cases, we can see the distinct tendencies of cicatricial healing as evidenced by the granulation tissues with many new capillaries invading into the center of lesions. (Fig. 11, 12)

It may be a reasonable presumption from the above pathologic-histological findings that these 3 cases would have been improved even radiographicaly, if the combined therapy had been continued for a longer period.

Therefore, it my be said that old tuberculin is one of the most useful irritating medical agent for sclerotic tuberculous lesions.

The radiographical findings of all 18 patients are shown in Table II. These

Table II. Radiographical Effect of Combined Theraphy with old Tuberculin and INH.

Type of Lesion		Total Nomber of Case	Radiographical Improvement	
			+	—
Non-Sclerotic	Caseous Lesion	0	0	0
	Cavity	1	1	0
Total		1	1	0
Sclerotic	Caseous Lesion	7	4	3 (1)
	Cavity	10	7 (2)	3 (2)
Total		17	11	6

The number in parentheses indicates the number of cases who were operated.

Table III. Comparison of Radiographical Effects of INH alone and Combination of old Tuberculin and INH on Sclerocaseous Lesions.

Method of Chemotherapy	Total Number of Cases	Radiographical Improvement	
		+	—
INH	18	2 (11%)	16
INH and Tuberculin	17	11 (64.6%)	6

INH alone·····INH 0.5 g daily for 4 months. For virgin cases.
INH and Tuberculin···INH 0.5 g daily for 4 months, old Tuberculin, ×1000, 0.5 cc intramuscularly 2 days a week for 1～3 month. For the cases who were treated with chemotherapy in the parst.

are the results in 4th month after the combined therapy except 5 cases who were operated in second or third month after the combined therapy and are shown in parenthesis.

As shown in Table II, 11 patients (64.6%) of 17 sclerotic cases improved clinically and in most cases the improvement in the roentgenslogical findings was recognized within one month after the start of treatment.

When we compare these results with those of INH alone for virgin cases which were already reported as one of the most excellent chemotherapy by us in another article[6], it is certain that the combined therapy with old tuberculin and INH is superior to INH alone for the sclerotic tuberculous lesions. (Table III)

Here it may be necessary to say that the tuberculin treatment has in itsself some disadvantages to the course of the disease, i.e., the new inflammation which is caused by tuberculin is essentially tuberculous in character, and the necrotic

and caseous substances will be formed if the adequate treatment do not be performed.

It has hitherto been said that the tuberculin therapy has a weak point of spreading or enlarging of the lesion during or after the treatment.

We hold the opinion in this point that such failures in the former tuberculin therapy were due to the lack of adequate regulation for the above reactions.

In our cases, we have experienced no case of uncontrolled spread of disease or enlargement of lesion during our treatment.

This may be attributable to INH treatment which was combined with tuberculin treatment, because INH is one of the most effective drugs for the acute tuberculous inflammation[5,8].

But, in our combined therapy, we think it is necessary to discontinue the administration of tuberculin for some period after the adequate treatment, because it needs for the lesion to promote the process of repairing after destruction by tuberculin to allow the cicatricial healing of lesion.

From our experience, after the combined therapy for 1 or 3 months the discontinuation of the tuberculin administration for 1 to 2 months may be necessary.

From the above results we believe that it may be recommended to use old tuberculin as the irritating agent with INH for the sclerotic tuberculous lesin which does not respond to any antituberculous agents available.

But during this combined therapy with old tuberculin and INH, we often encountered the undesirable side ractions as fever, general fatigue, headache, etc. in about 80% of the patients as shown in Table IV.

Table IV. Side Reactions during the Combined Therapy with old Tuberculin and INH.

Total Number of Cases	Side Reaction	
	+	−
18	14 (78%)	4 (22%)

Side Reaction	Cases	%
Fever	8	44.4
General Fatigue	7	38.9
Headache	6	33.3
Sleeplessness	1	5.6
Increase of Sputum	1	5.6
Increase of Cough	2	11.1
Gastroenteric Dysturbance	2	11.1

Therefore, we think that this therapy still has problems to be solved for the general clinical use.

If these harmful secondary reactions could be removed by some way, this therapy will becom a new useful treatment for the sclerotic tuberculous lesion.

We are now studying to solve these problems and the results will be reported later.

Conclusion

We have carried out clinical and pathologic-histological studies of the combined therapy with old tuberculin and INH, and have reached the following conclusions:

(1) The combined therapy of old tuberculin and INH is effective for the sclerotic caseous lesions which do not respond to antituberculous agents now available.

(2) It may be necessary in the combined treatment to have a cecession of tuberculin administration for 1-2 months after an adequate period of treatment.

(3) In general it is necessary to minimize in some way the side reactions which are experienced by tuberculin treatment, in order to use this treatment clinically in general.

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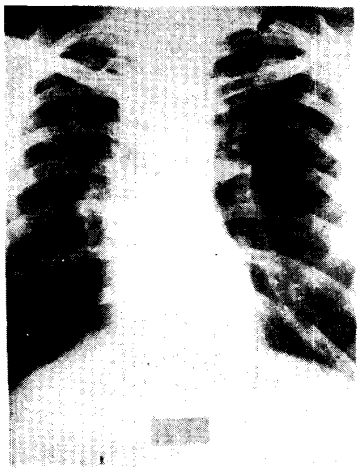

Fig. 1. (Case I).

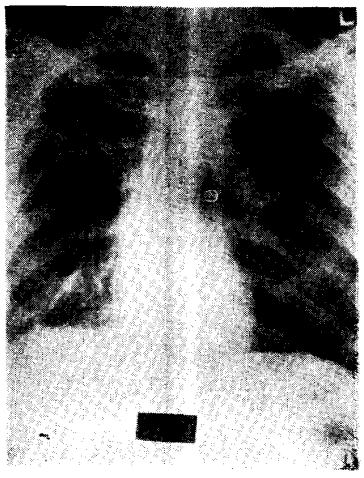

Fig. 2. (Case II).

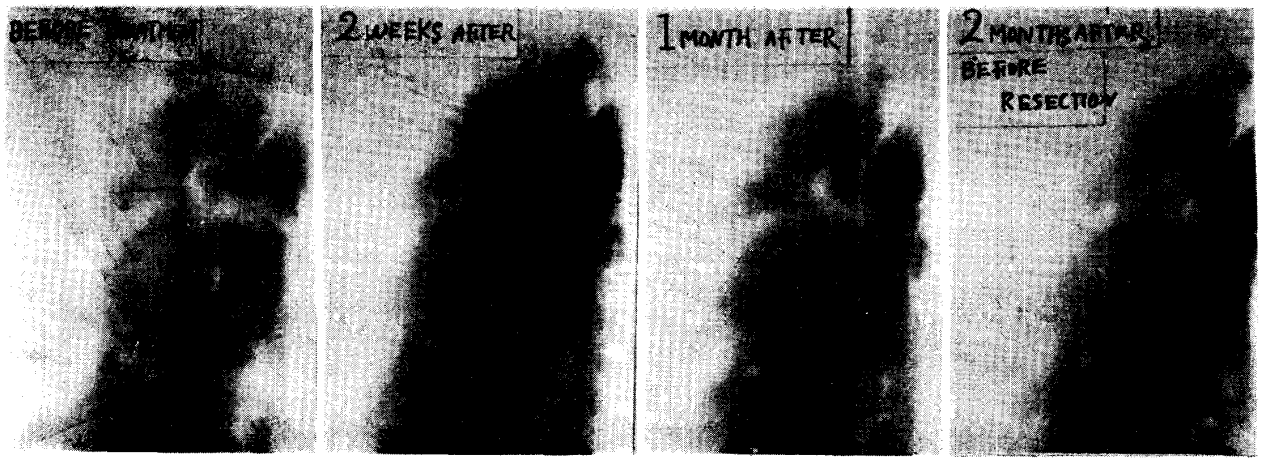

Fig. 3. Change of chest radiograph of Case I after treatment.

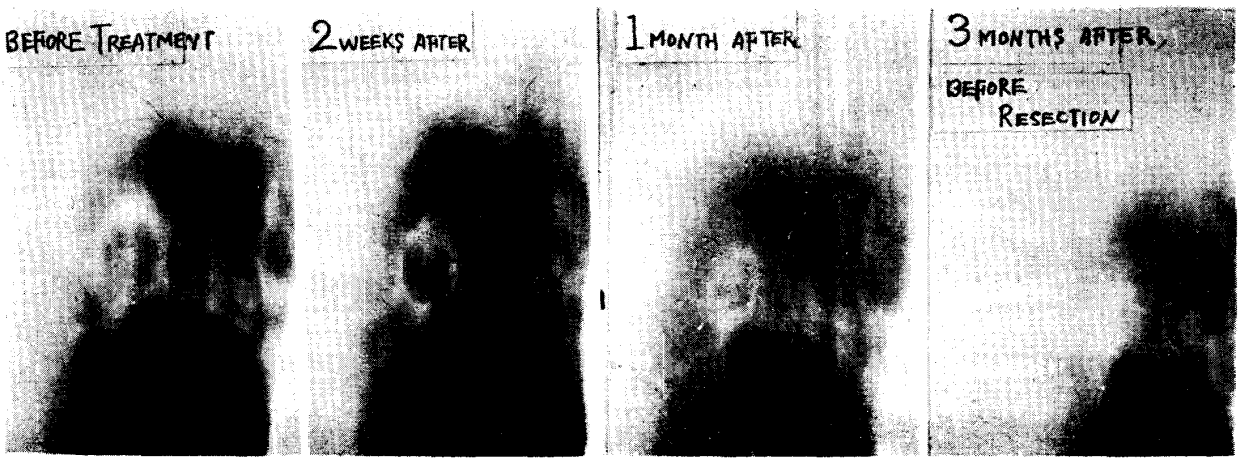

Fig. 4. Change of chest radiograph of Case II after treatment.

Fig. 5. Resected lung of Case I.

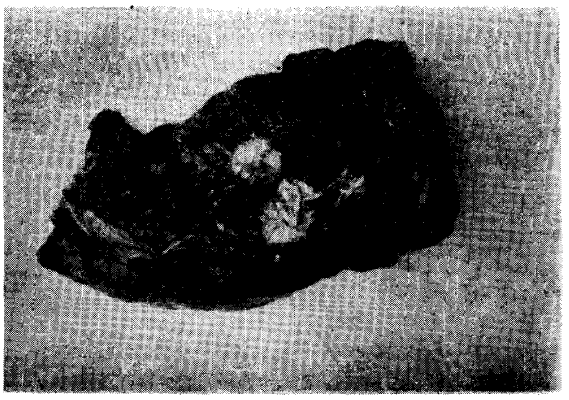

Fig. 6. Resected lung of Case II.

Fig. 7. Collargen fiber in cavity wall. (Chemotherapy alone)

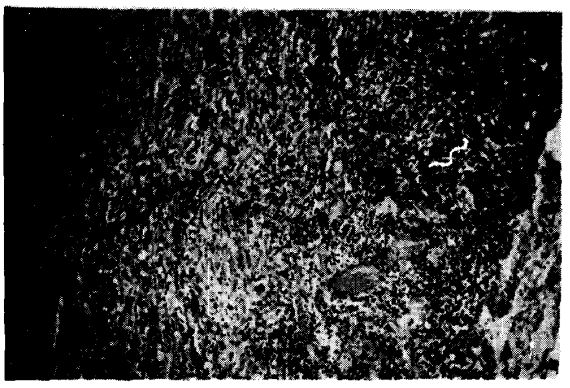

Fig. 8. Multiplication of capillaryies and cell infiltration in cavity wall. (Combined treatment)

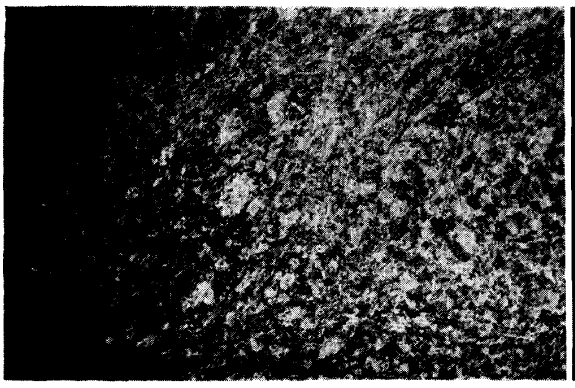

Fig. 9. Multiplication of capillaryies and cell infiltration in cavity wall. (Combined treatment)

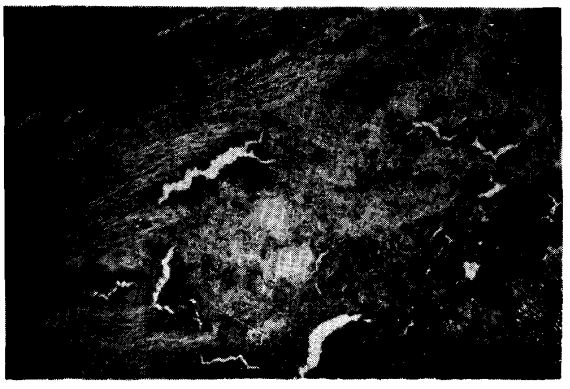

Fig. 10. Bleeding in cavity wall. (Combined treatment)

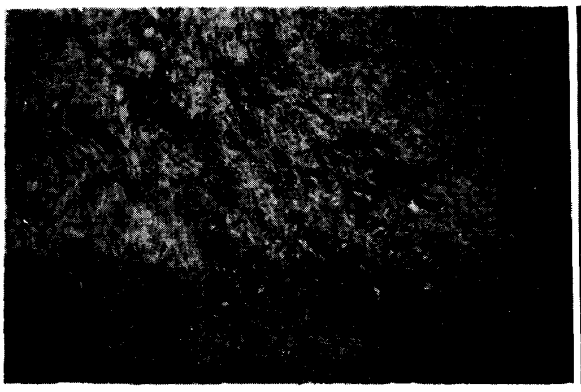

Fig. 11. Invasion of granulationstissue into lesions center. (Combined treatment)

Fig. 12. Granulations tissue accompanied with multiplication of capillaries. (Combined treatment)